

IONSYS- fentanyl hydrochloride patch

The Medicines Company

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use IONSYS safely and effectively. See full prescribing information for IONSYS.

IONSYS[®] (fentanyl iontophoretic transdermal system), CII

Initial U.S. Approval: 1968

WARNING: HOSPITAL USE ONLY; LIFE-THREATENING RESPIRATORY DEPRESSION; IONSYS REMS; ADDICTION, ABUSE, AND MISUSE; and CYTOCHROME P450 3A4 INTERACTION

See full prescribing information for complete boxed warning.

- Use of IONSYS may result in potentially life-threatening respiratory depression and death. Only the patient should activate dosing. (2.1, 5.1)
- Accidental exposure to an intact IONSYS or to the hydrogel component, especially by children, through contact with skin or mucous membranes, can result in a fatal overdose of fentanyl. (5.1)
- IONSYS is for use only in patients in the hospital. Discontinue IONSYS before patients leave the hospital. (5.1)
- Because of potentially life-threatening respiratory depression resulting from accidental exposure, IONSYS is only available through a restricted program called the IONSYS REMS Program. (5.2)
- IONSYS exposes users to risks of addiction, abuse, and misuse, which can lead to overdose and death. Assess patient's risk before prescribing, and monitor regularly for these behaviors or conditions. (5.3)
- Initiation of CYP 3A4 inhibitors or discontinuation of CYP 3A4 inducers can result in a fatal overdose of fentanyl from IONSYS. (5.15, 7.3, 12.3)

RECENT MAJOR CHANGES

Boxed Warning 04/2015

Indications and Usage (1) 04/2015

Dosage and Administration (2) 04/2015

Contraindications (4) 04/2015

Warnings and Precautions (5) 04/2015

INDICATIONS AND USAGE

IONSYS contains fentanyl, an opioid agonist. IONSYS is indicated for the short-term management of acute postoperative pain in adult patients requiring opioid analgesia in the hospital. (1)

Limitations of Use:

- Only for use in patients who are alert enough and have adequate cognitive ability to understand the directions for use. (1)
- Not for home use. IONSYS is for use only in patients in the hospital. Discontinue treatment with IONSYS before patients leave the hospital. (1)
- IONSYS is for use after patients have been titrated to an acceptable level of analgesia using alternate opioid analgesics. (1)

DOSAGE AND ADMINISTRATION

- Do not use more than one IONSYS at a time. (2.1)
- Patients should be titrated to comfort before initiating IONSYS. (2.2)
- For transdermal use only. Apply one IONSYS to intact, non-irritated, and non-irradiated skin on the chest or upper outer arm. (2.2, 2.3)
- Each IONSYS operates up to 24 hours or 80 doses, whichever comes first. IONSYS may be used for a maximum of 72 hours of therapy for acute postoperative pain, with each subsequent IONSYS applied to a different skin site. (2.2, 2.3)
- See full prescribing information for detailed instructions concerning administration, disposal and discontinuation of IONSYS. (2.3, 2.4, 2.5, 2.6)
- See *IONSYS Important Device Instructions* for additional details including troubleshooting device malfunction.

DOSAGE FORMS AND STRENGTHS

Iontophoretic transdermal system provides up to 80 doses (40 mcg each) of fentanyl per activation on-demand. (3)

CONTRAINDICATIONS

- Significant respiratory depression. (4)
- Acute or severe bronchial asthma. (4)

- Known or suspected paralytic ileus and GI obstruction. (4)
- Hypersensitivity to fentanyl, cetylpyridinium chloride (e.g., Cepacol[®]), or any components of IONSYS. (4)

----- WARNINGS AND PRECAUTIONS -----

- Interactions with CNS depressants: Concomitant use may cause hypotension, profound sedation, respiratory depression, and death. Monitor patients closely if co-administration is required. (5.1, 5.4, 7.1)
- Risk of injury during MRI: IONSYS contains metal parts and must be removed before an MRI. (5.5)
- Risk of use during other procedures (cardioversion, defibrillation, X-ray, CT, diathermy): Remove IONSYS before these procedures. (5.6)
- Topical skin reactions: If reaction is severe, discontinue IONSYS. (5.7)
- Elderly, cachectic, and debilitated patients, and those with chronic pulmonary disease: Monitor closely because of increased risk of life-threatening respiratory depression. (5.8, 5.9)
- Hypotension: Monitor during dose initiation. Avoid use of IONSYS in patients with circulatory shock. (5.10)
- Patients with head injury or increased intracranial pressure: Monitor for sedation and respiratory depression. Avoid use of IONSYS in patients with impaired consciousness or coma. Opioids may obscure clinical course in patients with head injury. (5.11)
- Patients with biliary tract disease, including acute pancreatitis: Monitor for worsening symptoms. (5.12)
- Increased risk of seizures in patients with seizure disorders: Monitor for worsened seizure control during IONSYS therapy. (5.13)
- Bradycardia: Closely monitor patients with bradyarrhythmias. (5.14)

----- ADVERSE REACTIONS -----

Most common (frequency $\geq 2\%$) adverse reactions were headache, hypotension, nausea, vomiting, anemia, dizziness, application site reaction-erythema, pruritus, and urinary retention. (6)

To report SUSPECTED ADVERSE REACTIONS, contact The Medicines Company at 1-877-488-6835 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----- DRUG INTERACTIONS -----

- Muscle relaxants: Monitor patients receiving muscle relaxants and IONSYS for signs of respiratory depression that may be greater than otherwise expected. (7.2)
- Monoamine oxidase inhibitors (MAOIs): Avoid use of IONSYS in patients taking MAOIs or within 14 days of stopping such treatment. (7.4)
- Mixed agonist/antagonist and partial agonist analgesics: Avoid use with IONSYS because they may reduce the analgesic effect of IONSYS or precipitate withdrawal. (7.5)

----- USE IN SPECIFIC POPULATIONS -----

Hepatic impairment and/or renal impairment: Monitor for signs of sedation and respiratory depression. (5.16, 5.17, 8.6, 8.7)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 5/2015

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FULL PRESCRIBING INFORMATION

WARNING: HOSPITAL USE ONLY; LIFE-THREATENING RESPIRATORY DEPRESSION; IONSYS REMS; ADDICTION, ABUSE, AND MISUSE; and CYTOCHROME P450 3A4 INTERACTION

Life-Threatening Respiratory Depression

- Use of IONSYS may result in potentially life-threatening respiratory depression and death as a result of the active drug, fentanyl. Only the patient should activate IONSYS dosing [see *Dosage and Administration (2.1)* and *Warnings and Precautions (5.1)*].
- Accidental exposure to an intact IONSYS or to the hydrogel component, especially by children, through contact with skin or contact with mucous membranes, can result in a fatal overdose of fentanyl [see *Warnings and Precautions (5.1)*].
- IONSYS is for use only in patients in the hospital. Discontinue treatment with IONSYS before patients leave the hospital [see *Warnings and Precautions (5.1)*].

IONSYS Risk Evaluation and Mitigation Strategy (REMS) Program

- Because of potentially life-threatening respiratory depression resulting from accidental exposure, IONSYS is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the IONSYS REMS Program [see *Warnings and Precautions (5.2)*].

Addiction, Abuse, and Misuse

- IONSYS exposes users to risks of addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk before prescribing, and monitor regularly for development of these behaviors or conditions [see *Warnings and Precautions (5.3)*].

Cytochrome P450 3A4 Interaction

- The concomitant use of IONSYS with all cytochrome P450 3A4 inhibitors may result in an increase in fentanyl plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression. In addition, discontinuation of a concomitantly used cytochrome P450 3A4 inducer may result in an increase in fentanyl plasma concentration. Monitor patients receiving IONSYS and any CYP3A4 inhibitor or inducer [see *Warnings and Precautions (5.15)*, *Drug Interactions (7.3)*, and *Clinical Pharmacology (12.3)*].

1. INDICATIONS AND USAGE

IONSYS is indicated for the short-term management of acute postoperative pain in adult patients requiring opioid analgesia in the hospital.

Limitations of Use:

- Only for use in patients who are alert enough and have adequate cognitive ability to understand the directions for use.
- Not for home use. IONSYS is for use only in patients in the hospital. Discontinue treatment with IONSYS before patients leave the hospital.

- IONSYS is for use after patients have been titrated to an acceptable level of analgesia using alternate opioid analgesics.

2. DOSAGE AND ADMINISTRATION

2.1 Important Administration Instructions

IONSYS is for hospital use only by patients under medical supervision and direction. Prior to the patient leaving the hospital, medical personnel must remove IONSYS and dispose of it properly [see Dosage and Administration (2.3, 2.4)].

Only the patient may activate IONSYS.

Only one IONSYS may be applied at a time. If inadequate analgesia is achieved with one IONSYS, either provide additional supplemental analgesic medication or replace with an alternate analgesic medication.

IONSYS should be prescribed only by persons knowledgeable in the administration of potent opioids and in the management of patients receiving potent opioids for treatment of pain. Patients treated with IONSYS should be under the supervision of medical personnel with expertise in the detection and management of hypoventilation including close observation, supportive measures, and use of opioid antagonists, depending on the patient's clinical status [see Overdosage (10.2)].

Remove and properly dispose of IONSYS prior to MRI, cardioversion, defibrillation, or diathermy [see Warnings and Precautions (5.5, 5.6)].

Avoid contact with synthetic materials (such as carpeted flooring) while assembling IONSYS and avoid exposing IONSYS to electronic security systems [see Warnings and Precautions (5.6)].

Depending on the rated maximum output power and frequency of the transmitter, the recommended separation distance between IONSYS and communications equipment or a Radio Frequency Identification (RFID) transmitter ranges between 0.12 and 23 meters [see Warnings and Precautions (5.6)].

See *IONSYS Important Device Instructions* for additional details, including information on troubleshooting device malfunction, recommended separation distances, and electromagnetic compatibility.

2.2 Dosage

IONSYS (see Figure 1A) is for use only after patients have been titrated to an acceptable level of analgesia using another opioid analgesic. Apply one IONSYS to healthy, unbroken/intact, non-irritated, and non-irradiated skin on the chest or upper outer arm ONLY.

IONSYS provides a 40 mcg dose of fentanyl per activation. It is important to instruct patients how to operate IONSYS to self-administer doses of fentanyl as needed to manage their acute, short-term, postoperative pain. Allow only the patient to self-administer doses of IONSYS. Each on-demand dose is delivered over a 10-minute period.

To initiate administration of IONSYS, the patient must press and release the button twice within 3 seconds. One single audible beep indicates the start of delivery of each dose. The green light will start blinking rapidly and the digital display will alternate between a walking circle and the number of doses delivered. When the 10-minute dose is complete, the green light will blink at a slow rate and the display will show the number of doses delivered (see Figure 1B).

Figure 1A: IONSYS Components

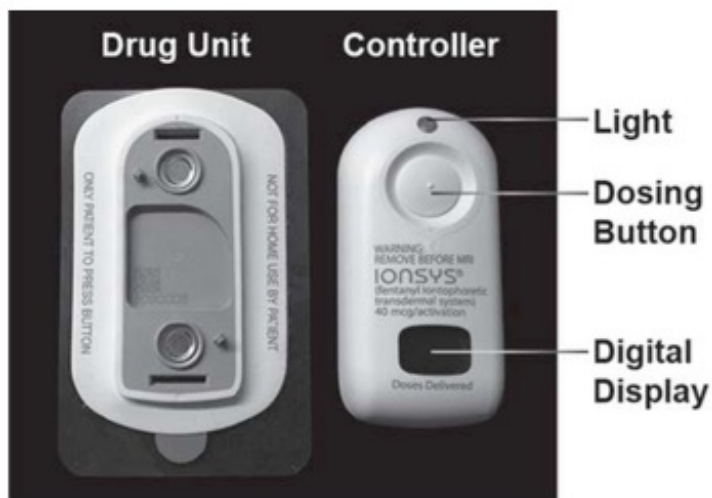
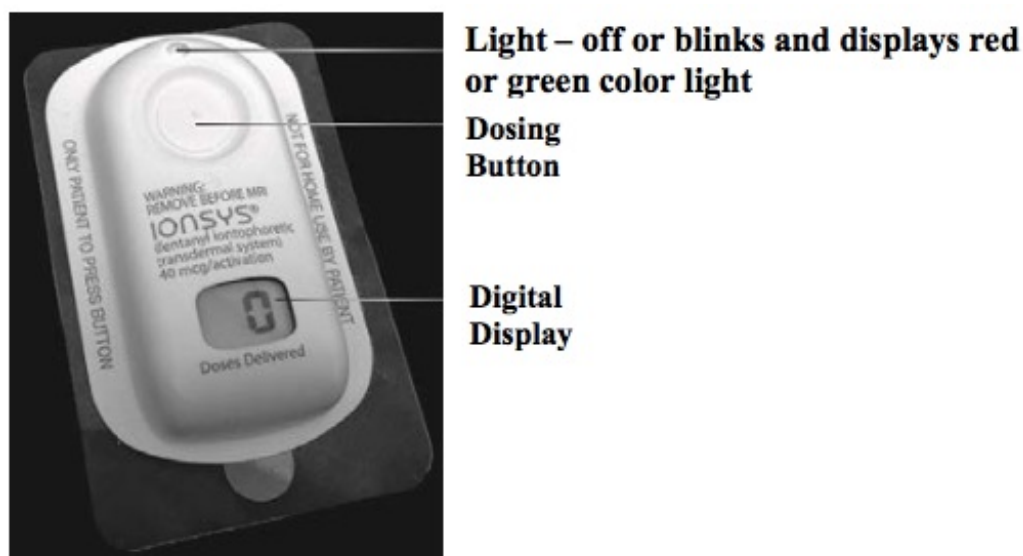


Figure 1B: Assembled IONSYS



A maximum of six 40-mcg doses per hour can be administered by IONSYS. The maximum amount of fentanyl that can be administered from a single IONSYS over 24 hours is 3.2 mg (eighty 40-mcg doses). Each IONSYS operates up to 24 hours or 80 doses, whichever comes first. Use one IONSYS at a time for up to 24 hours or 80 doses, whichever comes first. IONSYS may be used for a maximum of 3 days (72 hours) of therapy for acute postoperative pain, with each subsequent IONSYS applied to a different skin site [see *Dosage and Administration* (2.3)].

After the 24 hours have elapsed, or 80 doses have been delivered, IONSYS will not deliver any additional doses. The light and audible beep will not function. The digital display will continue to show the number of doses delivered for an additional 12 hours. If the patient tries to initiate a dose, IONSYS will ignore the dose request.

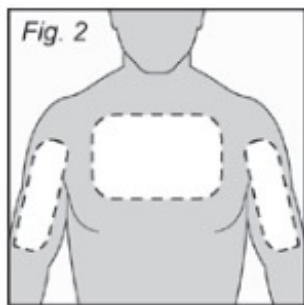
2.3 Administration of IONSYS

For SINGLE-USE only: operates up to 24 hours or 80 doses, whichever comes first.

FOR TRANSDERMAL USE ONLY

Preparation of Patient Site

1. Choose healthy, unbroken skin on the upper outer arm or chest ONLY (see Figure 2). IONSYS may only be applied to one of the three sites shown in Figure 2.



2. Clip excessive hair if necessary. Do not shave as this may irritate skin.
3. Clean the site with alcohol and let it dry. Do not use soaps, lotions, or other agents.

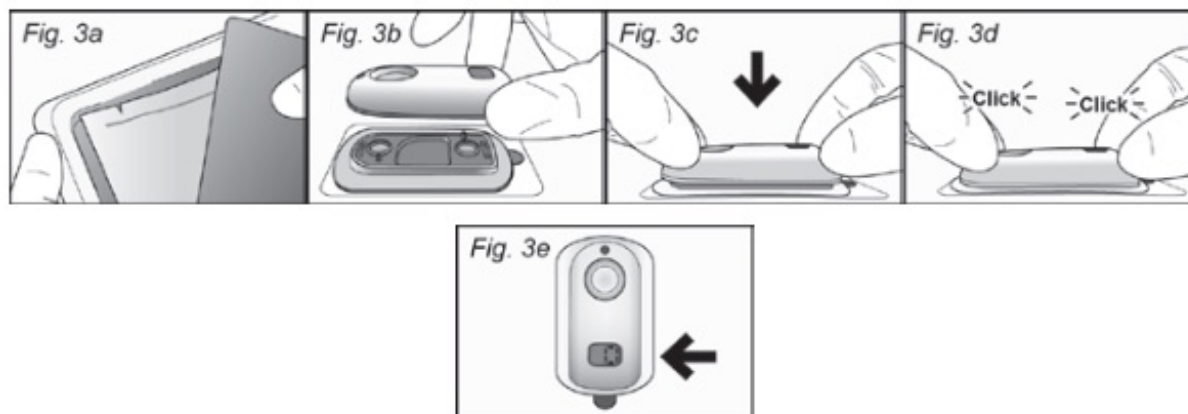
Assembly of IONSYS

DO NOT USE IONSYS if the seal on the Tray or Drug Unit pouch is broken or damaged.

Always wear gloves when handling IONSYS.

Complete these steps before applying IONSYS to the patient:

1. Open the tray by peeling back the tray lid (see Figure 3a). Remove the foil (drug) pouch and the Controller. Open the pouch containing the Drug Unit starting at the pre-cut notch and then carefully tearing along the top of the pouch.
2. Remove the Drug Unit from the pouch and place on a hard, flat surface.
3. Align the matching shapes of the Controller and the Drug Unit (see Figure 3b).
4. Press on both ends of the device to ensure that the snaps at both ends are fully engaged (see Figure 3c). You should hear one or two clicks when the snaps are fully engaged (see Figure 3d).
5. Once assembled, the digital display of the Controller will complete a short self-test during which there will be one audible beep, the red light will blink once, and the digital display will flash the number “88”. At the end of the self-test, the display will show the number “0” and a green light will blink at a slow rate to indicate IONSYS is ready for application (see Figure 3e).

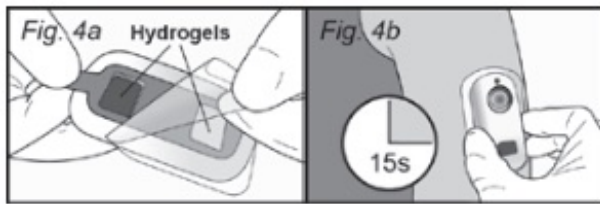


Application of IONSYS

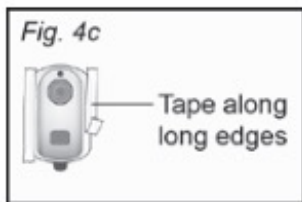
Always wear gloves when handling IONSYS.

Peel off and discard only the clear plastic liner covering the adhesive and hydrogels (see Figure 4a). Take care not to pull on the red tab while removing the clear plastic liner when preparing to apply IONSYS to the patient. The red tab is only to be used when separating IONSYS for disposal [see *Dosage and Administration* (2.4)].

Press and hold IONSYS firmly in place, with the sticky side down, onto patient’s skin for at least 15 seconds (see Figure 4b). Press with your fingers around the edges to be sure IONSYS adheres to the skin. Do not press the dosing button.



Occasionally, IONSYS may loosen from the skin; if this occurs, secure it to patient's skin by pressing the edges with fingers or securing with a non-allergenic tape to be sure that all edges make complete contact with the skin. If using tape, apply tape along the long edges to secure IONSYS to patient's skin (see Figure 4c). Do not tape over the button, the light, or the digital display. Do not tape if evidence of blistered or broken skin.



After taping, if IONSYS beeps again, remove and dispose. Place a new IONSYS on a different skin site. Each IONSYS may be used for up to 24 hours from the time it is assembled or until 80 doses have been administered, whichever comes first.

Operation of IONSYS

A recessed button is located on the top housing of IONSYS. To initiate administration of a fentanyl dose, the patient must press and release the button twice within 3 seconds. IONSYS should only be activated by the patient. One single audible beep indicates the start of delivery of each dose. The green light will start blinking rapidly and the digital display will alternate between a walking circle (see Figure 5) and the number of doses delivered.



Each dose will be delivered over 10-minutes. During this time IONSYS is locked-out and will not respond to additional button presses. When the 10-minute dose is complete, the green light will return to a slow rate of blinking and the display will show the number of doses delivered. IONSYS is now ready to be used again by the patient. The next dose cannot begin until the previous 10-minute delivery cycle is complete. Pressing the button during delivery of a dose will not result in additional drug being administered.

A healthcare professional must observe the first dose administered to ensure that the patient understands how to operate IONSYS and that IONSYS is working properly.

Each IONSYS will cease functioning at the end of 24 hours of use, or after 80 doses have been administered, whichever comes first. The green light will turn off and the number of doses delivered will flash on and off. The flashing digital display may be turned off by pressing and holding the dosing button for 6 seconds.

See *IONSYS Important Device Instructions* for additional details, including information on troubleshooting device malfunction.

Removal of IONSYS

Always wear gloves when handling IONSYS.

IONSYS may be removed at any time. However, once IONSYS has been removed, the same IONSYS must not be reapplied.

At the end of 24 hours of use, or after 80 doses have been delivered, IONSYS will deactivate and should be removed from the patient's skin. With gloves on, remove IONSYS from the patient (see Figure 6).



IONSYS contains two hydrogels (see Figure 4a), one of which contains fentanyl [see Description (11.2)]. Ensure both hydrogels remain with the removed IONSYS. If the hydrogel becomes separated from IONSYS during removal, **use gloves or tweezers to remove the hydrogel from the skin** and properly dispose of in accordance with state and federal regulations for controlled substances. If the patient requires additional analgesia a new IONSYS should be applied. In this case, IONSYS should be applied to a new skin site on the upper outer arm or chest.

One of the hydrogels contains fentanyl; take care not to touch the exposed hydrogel compartments or the adhesive (see Figure 4a). If a hydrogel drug reservoir is touched accidentally, rinse the area thoroughly with water (do not use soap).

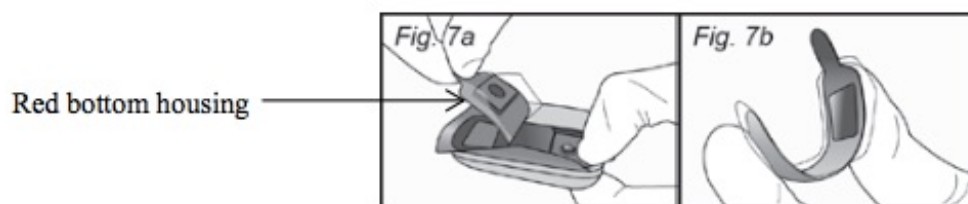
2.4 Disposal of IONSYS

Always wear gloves when handling IONSYS.

Contact with the hydrogels contained in IONSYS can result in a fatal overdose of fentanyl. Handle the used IONSYS by the sides and top while avoiding contact with the hydrogel. Dispose of IONSYS in accordance with state and federal regulations for controlled substances. The used red bottom housing (see Figure 7a) of IONSYS contains a significant amount of fentanyl that could cause a fatal overdose of fentanyl.

To dispose of a used IONSYS:

1. With gloves on, pull the red tab to separate the red bottom housing containing fentanyl from IONSYS (see Figure 7a).
2. Fold the red housing in half with the sticky side facing in (see Figure 7b).
3. Dispose of the folded over red housing containing the residual fentanyl per the institution's procedures for disposal of Schedule II drugs or by flushing it down the toilet.
4. Hold down dosing button until the display goes blank and then dispose of the remaining part of IONSYS containing electronics in waste designated for batteries.



2.5 Discontinuation of IONSYS

To discontinue use of IONSYS, remove and dispose of IONSYS according to the preceding directions.

2.6 Conversion from IONSYS to Alternate Analgesics

Upon discontinuation of IONSYS, if upon evaluation, conversion to an alternate analgesic is required, titrate the dose of the new analgesic, based upon the patient's report of pain, until adequate analgesia has been obtained, keeping in mind that the serum fentanyl concentration will decrease slowly following removal of IONSYS [see *Clinical Pharmacology* (12.3) and *Warnings and Precautions* (5)]. During the period of converting analgesics, monitor the patient for signs of respiratory and central nervous system depression.

3. DOSAGE FORMS AND STRENGTHS

Iontophoretic transdermal system provides up to 80 doses (40 mcg each) of fentanyl per activation on-demand [see *Description* (11) and *How Supplied/Storage and Handling* (16)].

4. CONTRAINDICATIONS

IONSYS is contraindicated in patients with:

- Significant respiratory depression
- Acute or severe bronchial asthma
- Known or suspected paralytic ileus and GI obstruction [see *Warnings and Precautions* (5.12)]
- Hypersensitivity to fentanyl, cetylpyridinium chloride (e.g., Cepacol[®]), or any components of IONSYS [see *Adverse Reactions* (6.1, 6.2)].

5. WARNINGS AND PRECAUTIONS

5.1 Life-Threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression has been reported with the use of opioids, including fentanyl, even when used as recommended. Respiratory depression from opioid use, including fentanyl, if not immediately recognized and treated, may lead to respiratory arrest and death. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient's clinical status [see *Overdosage* (10.2)]. Carbon dioxide (CO₂) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids.

The use of concomitant CNS-active drugs increases the risk of respiratory depression and requires special patient care and observation [see *Warnings and Precautions* (5.4)].

Keep IONSYS out of reach of children at all times.

Accidental exposure to an intact IONSYS or to its components, through contact with skin or mucous membranes can result in a fatal overdose of fentanyl. Following accidental contact with IONSYS or its components, immediately rinse the affected area thoroughly with water. Do not use soap, alcohol, or other solvent because they may enhance the drug's ability to penetrate the skin. The individual exposed should be monitored for signs of respiratory or central nervous system depression.

If IONSYS is not handled correctly using gloves, healthcare professionals are at risk of accidental exposure to a fatal overdose of fentanyl.

IONSYS is for hospital use only. Use of IONSYS outside of the hospital setting can lead to accidental exposure in others for whom it is not prescribed, causing fatal respiratory depression. Prior to the patient leaving the hospital, medical personnel must remove IONSYS and dispose of it properly.

5.2 IONSYS Risk Evaluation and Mitigation Strategy (REMS) Program

IONSYS is available only through a restricted program under a REMS called the IONSYS REMS Program because of the risk of respiratory depression resulting from accidental exposure [*see Warnings and Precautions (5.1)*].

Notable requirements of the IONSYS REMS Program include the following:

- Healthcare facilities that dispense and administer IONSYS must be certified in the IONSYS REMS program and comply with the REMS requirements.
- Hospitals must only dispense IONSYS for hospital use.

Further information about the IONSYS REMS Program is available at www.ionsysrems.com, or by calling 1-877-488-6835.

5.3 Addiction, Abuse, and Misuse

IONSYS contains fentanyl, an opioid agonist and a Schedule II controlled substance. Fentanyl can be abused in a manner similar to other opioid agonists, legal or illicit. Opioid agonists are sought by drug abusers and people with addiction disorders and are subject to criminal diversion. Consider these risks when prescribing or dispensing IONSYS in situations where the physician or pharmacist is concerned about an increased risk of addiction, abuse, and misuse. Concerns about addiction, abuse, and misuse, however, should not prevent the proper management of pain.

Assess each patient's risk for opioid abuse or addiction prior to prescribing IONSYS. The risk for opioid abuse is increased in patients with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depression). Patients at increased risk may still be appropriately treated with opioids; however these patients will require intensive monitoring for signs of misuse, abuse, or addiction. Routinely monitor all patients receiving opioids for signs of misuse, abuse, and addiction because these drugs carry a risk for addiction even under appropriate medical use.

Contact local State Professional Licensing Board or State Controlled Substances Authority for information on how to prevent and detect abuse or diversion of this product.

5.4 Interactions with Central Nervous System Depressants

Hypotension, profound sedation, coma, respiratory depression, and death may result if IONSYS is used concomitantly with alcohol or other central nervous system (CNS) depressants (e.g., sedatives, anxiolytics, hypnotics, neuroleptics, other opioids).

When considering the use of IONSYS in a patient taking a CNS depressant, assess the duration of use of the CNS depressant and the patient's response, including the degree of tolerance that has developed to CNS depression. Additionally, evaluate the patient's use of alcohol or illicit drugs that cause CNS depression [*see Drug Interactions (7.1)*].

5.5 Risk of Injury during Magnetic Resonance Imaging (MRI) Procedure

The IONSYS device is considered MR Unsafe. IONSYS contains metal parts and must be removed and properly disposed of before an MRI procedure to avoid injury to the patient and damage to IONSYS. It is unknown if exposure to an MRI procedure increases release of fentanyl from IONSYS. Monitor any patients wearing IONSYS with inadvertent exposure to an MRI for signs of central nervous system and

respiratory depression.

5.6 Risk of IONSYS Use during Other Procedures or Near Certain Equipment

Cardioversion, Defibrillation, Radiographic Imaging Procedures other than MRI, or Diathermy

Use of IONSYS during cardioversion, defibrillation, X-ray, CT, or diathermy can damage IONSYS from the strong electromagnetic fields set up by these procedures. IONSYS contains radio-opaque components and may interfere with an X-ray image or CT scan. Remove and properly dispose of IONSYS prior to cardioversion, defibrillation, X-ray, CT, or diathermy [see *Dosage and Administration* (2.3, 2.4)].

Synthetic Materials and Electronic Security Systems

Avoid contact with synthetic materials (such as carpeted flooring) to reduce the possibility of electrostatic discharge and damage to IONSYS. Avoid exposing IONSYS to electronic security systems to reduce the possibility of damage to IONSYS. See *IONSYS Important Device Instructions* for additional details.

Communications Equipment and Radio Frequency Identification Transmitters

Use of IONSYS near communications equipment (e.g., base stations for radio telephones and land mobile radios, amateur radio, AM and FM radio broadcast and TV broadcast Radio) and Radio Frequency Identification (RFID) transmitters can damage IONSYS. Depending on the rated maximum output power and frequency of the transmitter, the recommended separation distance between IONSYS and communications equipment or the RFID transmitter ranges between 0.12 and 23 meters. See *IONSYS Important Device Instructions* for detailed instructions regarding recommended separation distances.

Other Electromechanical Devices Including Pacemakers or Electrical Monitoring Equipment

The low-level electrical current provided by IONSYS does not result in electromagnetic interference with other electromechanical devices like pacemakers or electrical monitoring equipment.

If exposure to the procedures listed above, electronic security systems, electrostatic discharge, communications equipment, or RFID transmitters occurs, and if IONSYS does not appear to function normally [see *Dosage and Administration* (2.3)], remove IONSYS and replace with a new IONSYS. See *IONSYS Important Device Instructions* for additional details including information on troubleshooting device malfunction and electromagnetic compatibility.

5.7 Topical Skin Reactions

Topical skin reactions (erythema, sweating, vesicles, papules/pustules) may occur with use of IONSYS and are typically limited to the application site area. If a severe skin reaction is observed, remove IONSYS and discontinue further use.

5.8 Use in Elderly, Cachectic, and Debilitated Patients

Life-threatening respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients as they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients. Monitor such patients closely; especially when IONSYS is used concomitantly with other drugs that depress respiration [see *Warnings and Precautions* (5.1)].

5.9 Use in Patients with Chronic Pulmonary Disease

Monitor patients with significant chronic obstructive pulmonary disease or cor pulmonale, and patients having a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression for respiratory depression, particularly when initiating therapy with IONSYS, as in these patients, even usual therapeutic doses of IONSYS may decrease respiratory drive to the point of apnea [see *Warnings and Precautions* (5.1)]. Consider the use of alternative non-opioid analgesics in these patients if possible.

5.10 Hypotensive Effect

IONSYS may cause severe hypotension including orthostatic hypotension and syncope in ambulatory patients. There is increased risk in patients whose ability to maintain blood pressure has already been compromised by a reduced blood volume, or concurrent administration of certain CNS depressant drugs (e.g., phenothiazines or general anesthetics) [see *Drug Interactions* (7.1)]. Monitor these patients for signs of hypotension after initiating IONSYS. Avoid the use of IONSYS in patients with circulatory shock as IONSYS may cause vasodilation that can further reduce cardiac output and blood pressure.

5.11 Use in Patients with Head Injury or Increased Intracranial Pressure

IONSYS is not suitable for use in patients who are not alert and able to follow directions. Monitor patients using IONSYS who may be susceptible to the intracranial effects of CO₂ retention (e.g., those with evidence of increased intracranial pressure or brain tumors) for signs of sedation and respiratory depression, particularly when initiating therapy with IONSYS. IONSYS may reduce respiratory drive, and the resultant CO₂ retention can further increase intracranial pressure. Opioids, including IONSYS, may also obscure the clinical course in a patient with a head injury.

Avoid the use of IONSYS in patients with impaired consciousness or coma.

5.12 Use in Patients with Gastrointestinal Conditions

IONSYS is contraindicated in patients with gastrointestinal obstruction, including paralytic ileus. Fentanyl may cause spasm of the sphincter of Oddi. Monitor patients with biliary tract disease, including acute pancreatitis for worsening symptoms. Opioids, including IONSYS, may cause increases in serum amylase.

5.13 Use in Patients with Convulsive or Seizure Disorders

IONSYS may aggravate convulsions in patients with convulsive disorders, and may induce or aggravate seizures in some clinical settings. Monitor patients with a history of seizure disorders for worsened seizure control during IONSYS therapy.

5.14 Bradycardia

IONSYS may produce bradycardia in some patients. Monitor patients with bradyarrhythmias closely for changes in heart rate, particularly when initiating therapy with IONSYS.

5.15 Cytochrome P450 3A4 Inhibitors and Inducers

Since the CYP3A4 isoenzyme plays a major role in the metabolism of fentanyl, drugs that alter CYP3A4 activity may cause changes in clearance of fentanyl which could lead to changes in fentanyl plasma concentrations.

The concomitant use of IONSYS with a CYP3A4 inhibitor (such as ritonavir, ketoconazole, itraconazole, troleandomycin, clarithromycin, nelfinavir, nefazadone, amiodarone, amprenavir, aprepitant, diltiazem, erythromycin, fluconazole, fosamprenavir, verapamil) may result in an increase in fentanyl plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression. Carefully monitor patients receiving IONSYS and any CYP3A4 inhibitor for signs of sedation and respiratory depression for an extended period of time, and make dosage adjustments as needed.

If co-administration is necessary, caution is advised when initiating IONSYS treatment in patients currently taking, or discontinuing, CYP3A4 inhibitors or inducers. Evaluate these patients at frequent intervals and consider dose adjustments until stable drug effects are achieved [see *Drug Interactions* (7.3) and *Clinical Pharmacology* (12.3)].

5.16 Hepatic Impairment

Insufficient data are available on the use of IONSYS in patients with impaired hepatic function. Since fentanyl is eliminated by hepatic metabolism and fentanyl clearance may decrease in patients with hepatic disease, monitor patients with hepatic impairment for signs of sedation and respiratory depression [see *Use in Specific Populations* (8.6) and *Clinical Pharmacology* (12.3)].

5.17 Renal Impairment

A clinical pharmacology study with intravenous fentanyl in patients undergoing kidney transplantation has shown that patients with high blood urea nitrogen level had low fentanyl clearance. Monitor for signs of sedation and respiratory depression in patients with renal impairment [see *Use in Specific Populations* (8.7) and *Clinical Pharmacology* (12.3)].

6. ADVERSE REACTIONS

The following serious adverse reactions are described elsewhere in the labeling:

- Life-threatening respiratory depression [see *Warnings and Precautions* (5.1)]
- Addiction, abuse, and misuse [see *Warnings and Precautions* (5.3)]
- Interactions with other CNS depressants [see *Warnings and Precautions* (5.4)]
- Hypotensive effects [see *Warnings and Precautions* (5.10)]
- Gastrointestinal effects [see *Warnings and Precautions* (5.12)]
- Seizures [see *Warnings and Precautions* (5.13)]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In controlled and uncontrolled studies, the safety of IONSYS 40 mcg was evaluated in a total of 2114 patients with acute postoperative pain requiring opioid analgesia.

The most common adverse reactions ($\geq 2\%$) in the placebo-controlled studies, regardless of relationship to study medication, are listed in Table 1.

Table 1: Adverse Reactions with Incidence $\geq 2\%$ in Placebo-controlled Studies 1, 2, and 3 (N=791; 24 Hour Duration)

Adverse Reactions	IONSYS (n=475)	Placebo (n=316)
Body as a Whole		
Headache	9%	7%
Cardiovascular System		
Hypotension	2%	<1%
Digestive System		
Nausea	39%	22%
Vomiting	12%	6%
Hemic and Lymphatic System		
Anemia	3%	<1%
Nervous System		
Dizziness	3%	1%
Skin System		
Application site reaction- Erythema	14%	2%

Pruritus	6%	<1%
Urogenital System		
Urinary retention	3%	<1%

NOTE: Patients reported as having “Nausea and vomiting” are included in “Nausea” and “Vomiting” in Table 1.

Other Adverse Reactions

Other adverse reactions that were reported (excluding adverse reactions listed in Table 1) in 4 active comparator trials vs. IV PCA morphine in patients treated with IONSYS (n=1288) are described below:

Body as a Whole: abdominal pain, back pain, extremity pain, chest pain, chills, abdomen enlarged, asthenia, abscess, hypothermia

Cardiovascular System: syncope, postural hypotension, vasodilation, hypertension, atrial fibrillation, bradycardia, tachycardia, bigeminy, arrhythmia, myocardial infarct

Digestive System: constipation, flatulence, dyspepsia, ileus, dry mouth, diarrhea

Metabolic and Nutritional System: peripheral edema, healing abnormal, edema, dehydration

Musculoskeletal System: leg cramps and myalgia

Nervous System: insomnia, anxiety, somnolence, confusion, paresthesia, hypesthesia, nervousness, agitation, abnormal dreams, tremor

Respiratory System: hypoxia, hypoventilation, dyspnea, apnea, cough increased, asthma, hiccup, atelectasis, rhinitis, hyperventilation

Skin System: application site reactions including: itching, vesicles, papules/pustules, edema, pain, burning, dry and flaky skin, and vesiculobullous rash, wound site oozing/bleeding, wound site inflammation/erythema, rash, sweating

Special Senses: abnormal vision-blurred vision

Urogenital System: urination impaired, hematuria, urinary tract infection, urinary urgency, dysuria

Scheduled observation of the skin approximately 24 hours after IONSYS removal was included in several studies. Some redness at the skin sites was observed in approximately 60% of patients at this observation. The skin findings included erythema, edema, and papules. The majority of these events were categorized as mild. Two patients were noted to have hyperpigmentation lasting 2 – 3 weeks at the application site. Three patients noted a rectangular mark at the application site, which persisted for up to 3 months after study completion.

6.2 Post Marketing Experience

The following adverse reactions have been identified during post approval use of IONSYS. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

The most commonly observed events were related to application site reactions which included urticaria, application site discharge, erosion, hyperesthesia, pustules, rash and scab, application site bleeding, application site infection, and necrosis.

7. DRUG INTERACTIONS

7.1 Central Nervous System Depressants

The concomitant use of IONSYS with other central nervous system depressants including sedatives, hypnotics, tranquilizers, phenothiazines, general anesthetics, other opioids, and alcohol can increase the

risk of respiratory depression, profound sedation, coma, and death. Monitor patients receiving concomitant CNS depressants and IONSYS for signs of respiratory depression, sedation, and hypotension [*see Warnings and Precautions (5.4)*].

7.2 Muscle Relaxants

IONSYS may enhance the neuromuscular blocking action of true skeletal muscle relaxants and produce an increased degree of respiratory depression. Monitor patients receiving muscle relaxants and IONSYS for signs of respiratory depression that may be greater than otherwise expected.

7.3 Drugs Affecting CYP3A4 Isoenzyme System

Inhibitors of CYP3A4

Because the CYP3A4 isoenzyme plays a major role in the metabolism of fentanyl, drugs that inhibit CYP3A4 activity may cause decreased clearance of fentanyl which could lead to an increase in fentanyl plasma concentrations and result in increased or prolonged opioid effects. These effects could be more pronounced with concomitant use of 3A4 inhibitors. If coadministration with IONSYS is necessary, monitor patients for respiratory depression and sedation at frequent intervals and consider dose adjustments until stable drug effects are achieved [*see Clinical Pharmacology (12.3)*].

Inducers of CYP3A4

CYP450 3A4 inducers may induce the metabolism of fentanyl and, therefore, may cause increased clearance of the drug which could lead to a decrease in fentanyl plasma concentrations, lack of efficacy or, possibly, development of a withdrawal syndrome in a patient who has developed physical dependence to fentanyl. If co-administration with IONSYS is necessary, monitor for signs of opioid withdrawal and consider dose adjustments until stable drug effects are achieved [*see Clinical Pharmacology (12.3)*].

After stopping the treatment of a CYP3A4 inducer, as the effects of the inducer decline, the fentanyl plasma concentration will increase which could increase or prolong both the therapeutic and adverse effects, and may cause serious respiratory depression or death [*see Clinical Pharmacology (12.3)*].

7.4 Monoamine Oxidase (MAO) Inhibitors

Avoid use of IONSYS in patients who would require the concomitant administration of a monoamine oxidase (MAO) inhibitor, or within 14 days of stopping such a treatment because severe and unpredictable potentiation by MAO inhibitors has been reported with opioid analgesics.

7.5 Agonist/Antagonist and Partial Agonist Opioid Analgesics

Mixed agonist/antagonist (i.e., pentazocine, nalbuphine, and butorphanol) and partial agonist (buprenorphine) analgesics may reduce the analgesic effect of IONSYS or may precipitate withdrawal symptoms. Avoid the use of agonist/antagonist and partial agonist analgesics in patients receiving IONSYS.

7.6 Diuretics

IONSYS can reduce the efficacy of diuretics by inducing the release of antidiuretic hormone. IONSYS may also lead to acute retention of urine by causing spasm of the sphincter of the bladder, particularly in men with enlarged prostates.

7.7 Anticholinergics

Anticholinergics or other medications with anticholinergic activity when used concurrently with IONSYS may result in increased risk of urinary retention and/or severe constipation, which may lead to paralytic ileus. Monitor patients for signs of urinary retention or reduced gastrointestinal motility when IONSYS is used concurrently with anticholinergic drugs.

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no studies with the use of IONSYS in pregnant women. Limited published data on fentanyl use during pregnancy are insufficient to establish any drug-associated risks. In animal reproduction and developmental studies, at doses within the dosing range of humans, there was an increased risk for early embryonic lethality, decreased pup survival, and delays in developmental landmarks of surviving pups [*see Data*]. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Labor or Delivery

Opioids cross the placenta and may produce respiratory depression and psycho-physiologic effects in neonates. IONSYS is not recommended for use in women during or immediately prior to labor, when other analgesic techniques are more appropriate. Opioid analgesics, including IONSYS, can prolong labor through actions which temporarily reduce the strength, duration and frequency of uterine contractions. However, this effect is not consistent and may be offset by an increased rate of cervical dilation, which tends to shorten labor. Neonates, whose mothers received opioid analgesics during labor, must be observed closely for signs of respiratory depression. An opioid antagonist, such as naloxone, must be available for reversal of narcotic-opioid induced respiratory depression in the neonate.

Data

Animal Data

The potential effects of fentanyl on embryo-fetal development were studied in rat and rabbit models.

Published literature reports that administration of fentanyl (0, 0.01, 0.1, or 0.5 mg/kg/day) to pregnant female Sprague-Dawley rats from Gestation Day 7 to 21 via implanted microosmotic minipumps did not produce any evidence of teratogenicity. The high dose is approximately 1.5 times the daily maximum recommended human dose (MRHD) of 3.2 mg/day based on a mg/m² body surface area basis and a 60 kg human body weight.

In contrast, the intravenous administration of fentanyl at doses of 0, 0.01, or 0.03 mg/kg (equivalent to 0.03 and 0.09 times, respectively, the MHRD) to pregnant female rats from Gestation Day 6 to 18 resulted in evidence of embryo toxicity and a slight increase in mean delivery time in the 0.03 mg/kg/day group. There was no clear evidence of teratogenicity noted.

Pregnant female New Zealand White rabbits were treated with fentanyl (0, 0.025, 0.1, 0.4 mg/kg) via intravenous infusion from Gestation Day 6 to 18. Fentanyl produced a slight decrease in the body weight of the live fetuses at the high dose, which may be attributed to maternal toxicity (decreased body weight and sedation). Under the conditions of the assay, there was no evidence for fentanyl-induced adverse effects on embryo-fetal development at doses up to 0.4 mg/kg (2.4 times the MRHD).

The potential effects of fentanyl on prenatal and postnatal development were examined in the rat model. Pregnant female Wistar rats were treated with 0, 0.025, 0.1, or 0.4 mg/kg/day fentanyl via intravenous infusion (equivalent to 0.08, 0.3, and 1.2 times, respectively, the MRHD) from Gestation Day 6 through 3 weeks of lactation. Fentanyl treatment (0.4 mg/kg/day) significantly decreased body weight in male and female pups and also decreased survival in pups at Post-Natal Day 4. Both the mid-dose and high-dose of fentanyl animals demonstrated alterations in some physical landmarks of development (delayed incisor eruption and eye opening) and transient behavioral development (decreased locomotor activity at Post-Natal Day 28 which recovered by Post-Natal Day 50). No adverse effects were observed at 0.08 times the MRHD.

8.2 Lactation

Risk Summary

Limited published literature reports that fentanyl is present in human milk at low levels, which resulted in an estimated infant dose of 0.38% of the maternal weight-adjusted dosage. There are no reports of adverse effects on the breastfed infant and no information on the effects on milk production. The developmental and health benefits from breastfeeding should be considered along with the mother's need for IONSYS and any potential effects on the breastfed infant from IONSYS or from the underlying maternal condition.

8.4 Pediatric Use

The efficacy and safety of IONSYS have not been established in pediatric patients under 18 years of age.

8.5 Geriatric Use

IONSYS 40 mcg has been studied in 499 patients 65 years or older; 174 of whom were 75 years or older. No major differences in safety or effectiveness were observed between these subjects and younger subjects. However, the incidence of the following events was slightly higher ($\geq 1\%$) in patients ≥ 65 years compared with patients who were 18 to 64 years of age: hypotension (4% versus 3%), confusion (2% versus $< 1\%$), hypokalemia (3% versus 1%), hypoxia (3% versus 2%), and hypoventilation (2% versus $< 1\%$).

In a pharmacokinetic study of IONSYS conducted in 63 healthy volunteers (25 subjects older than 65 years), age did not significantly affect the extent of drug absorption. Literature suggests that the clearance of fentanyl may be reduced and the terminal half-life prolonged in the elderly.

Monitor geriatric patients closely for signs of sedation and respiratory depression, particularly when initiating therapy with IONSYS and when given in conjunction with other drugs that depress respiration [*see Warnings and Precautions (5.1, 5.8)*].

8.6 Hepatic Impairment

Insufficient data are available on the use of IONSYS in patients with impaired hepatic function. Since fentanyl is eliminated by hepatic metabolism and fentanyl clearance may decrease in patients with hepatic disease, monitor patients with hepatic impairment closely for signs of central nervous system and respiratory depression, especially when initiating treatment with IONSYS.

8.7 Renal Impairment

Approximately 10% of administered fentanyl is excreted unchanged by the kidney. Insufficient data are available on the use of IONSYS in patients with impaired renal function to determine effects on renal clearance of fentanyl. Monitor patients with renal impairment closely for signs of central nervous system and respiratory depression, especially when initiating treatment with IONSYS.

9. DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

IONSYS contains fentanyl, a Schedule II controlled substance with a high potential for abuse similar to other opioids including morphine, hydromorphone, methadone, oxycodone, and oxymorphone. IONSYS can be abused and is subject to misuse, addiction, and criminal diversion [*see Warnings and Precautions (5.3)*].

9.2 Abuse

All patients treated with opioids require careful monitoring for signs of abuse and addiction, since use of opioid analgesic products carries the risk of addiction even under appropriate medical use.

Drug abuse is the intentional non-therapeutic use of an over-the-counter or prescription drug, even once, for its rewarding psychological or physiological effects. Drug abuse includes, but is not limited to, the following examples: the use of a prescription or over-the-counter drug to get “high”, or the use of steroids for performance enhancement and muscle build up.

Drug addiction is a cluster of behavioral, cognitive, and physiological phenomena that develop after repeated substance use and include: a strong desire to take the drug, difficulties in controlling its use, persisting in its use despite harmful consequences, a higher priority given to drug use than to other activities and obligations, increased tolerance, and sometimes a physical withdrawal.

“Drug-seeking” behavior is very common in addicts and drug abusers. Drug-seeking tactics include emergency calls or visits near the end of office hours, refusal to undergo appropriate examination, testing or referral, repeated “loss” of prescriptions, tampering with prescriptions and reluctance to provide prior medical records or contact information for other treating physician(s). “Doctor shopping” to obtain additional prescriptions is common among drug abusers and people suffering from untreated addiction.

Abuse and addiction are separate and distinct from physical dependence and tolerance. Physicians should be aware that addiction may not be accompanied by concurrent tolerance and symptoms of physical dependence in all addicts. In addition, abuse of opioids can occur in the absence of true addiction.

IONSYS, like other opioids, can be diverted for non-medical use into illicit channels of distribution. Careful record-keeping of prescribing information, including quantity and frequency is strongly advised.

Proper assessment of the patient, proper prescribing practices, periodic re-evaluation of therapy, and proper dispensing and storage are appropriate measures that help to limit abuse of opioid drugs.

Risks Specific to Abuse of IONSYS

IONSYS is for transdermal use only for patients in the hospital. Abuse of IONSYS poses a risk of overdose and death. This risk is increased with concurrent abuse of IONSYS and alcohol and other central nervous system depressants [see *Warnings and Precautions (5.3, 5.4) and Drug Interactions (7.1)*]. Contact with residual fentanyl in hydrogel of the device can result in fatal overdose.

Access to abusable drugs such as IONSYS presents a risk for abuse and diversion in the health care community. Implementation of effective accounting procedures in addition to routine procedures for handling controlled substances may minimize these risks.

Healthcare professionals should contact their State Professional Licensing Board or State Controlled Substances Authority for information on how to prevent and detect abuse or diversion of this product.

9.3 Dependence

Both tolerance and physical dependence can develop during chronic opioid therapy. Tolerance is the need for increasing doses of opioids to maintain a defined effect such as analgesia (in the absence of disease progression or other external factors). Tolerance may occur to both the desired and undesired effects of drugs, and may develop at different rates for different effects.

Physical dependence results in withdrawal symptoms after abrupt discontinuation or a significant dose reduction of a drug. Withdrawal may also be precipitated through the administration of drugs with opioid antagonist activity, e.g., naloxone, nalmefene, mixed agonist/antagonist analgesics (pentazocine, butorphanol, malbuphine), or partial agonists (buprenorphine). Physical dependence may not occur to a clinically significant degree until after several days to weeks of continued opioid usage. Some or all of the following can characterize this syndrome: restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, myalgia, and mydriasis. Other signs and symptoms also may develop, including:

irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea, or increased blood pressure, respiratory rate, or heart rate.

Infants born to mothers physically dependent on opioids will also be physically dependent and may exhibit respiratory difficulties and withdrawal symptoms [see *Use in Specific Populations* (8.1)].

10. OVERDOSAGE

10.1 Clinical Presentation

Acute overdose with IONSYS can be manifested by respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, and in some cases, pulmonary edema, bradycardia, hypotension, partial or complete airway obstruction, atypical snoring, and death. Marked mydriasis rather than miosis may be seen with hypoxia in overdose situations [see *Clinical Pharmacology* (12.2)].

10.2 Treatment of Overdose

In case of overdose, priorities are the reestablishment of a patent and protected airway and institution of assisted or controlled ventilation if needed. Employ other supportive measures (including oxygen and vasopressors) in the management of circulatory shock and pulmonary edema accompanying overdose as indicated. Cardiac arrest or arrhythmias will require advanced life support techniques.

The opioid antagonists naloxone or nalmefene, are specific antidotes to respiratory depression resulting from opioid overdose. Opioid antagonists should not be administered in the absence of clinically significant respiratory or circulatory depression secondary to fentanyl overdose. Such agents should be administered cautiously to patients who are known, or suspected to be, physically dependent on opioids. In such cases, an abrupt or complete reversal of opioid effects may precipitate an acute withdrawal syndrome.

Because the duration of reversal is expected to be less than the duration of action of fentanyl, carefully monitor the patient until spontaneous respiration is reliably re-established. If the response to opioid antagonists is suboptimal or only brief in nature, administer additional antagonist as directed by the product's prescribing information.

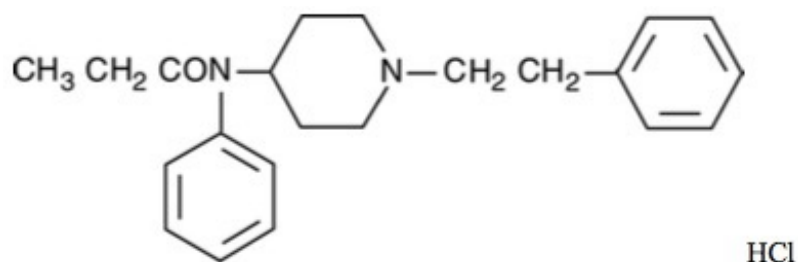
In an individual physically dependent on opioids, administration of the usual dose of the antagonist may precipitate acute withdrawal. The severity of the withdrawal symptoms experienced will depend on the degree of physical dependence and the dose of the antagonist administered. If a decision is made to treat serious respiratory depression in the physically dependent patient, administration of the antagonist should be begun with care and by titration with smaller than usual doses of the antagonist.

11. DESCRIPTION

11.1 Chemical Characteristics of Drug Substance and Product

IONSYS (fentanyl iontophoretic transdermal system) is a patient-controlled iontophoretic transdermal system providing on-demand systemic delivery of fentanyl, an opioid agonist, for up to 24 hours or a maximum of 80 doses, whichever comes first.

The chemical name is propanamide, N-phenyl-N-[1-(2-phenylethyl)-4- piperidinyl] monohydrochloride. The structural formula is:



The molecular weight of fentanyl hydrochloride is 372.93, and the empirical formula is $C_{22}H_{28}N_2O \cdot HCl$. The n-octanol:water partition coefficient is 860:1; the pKa is 8.4.

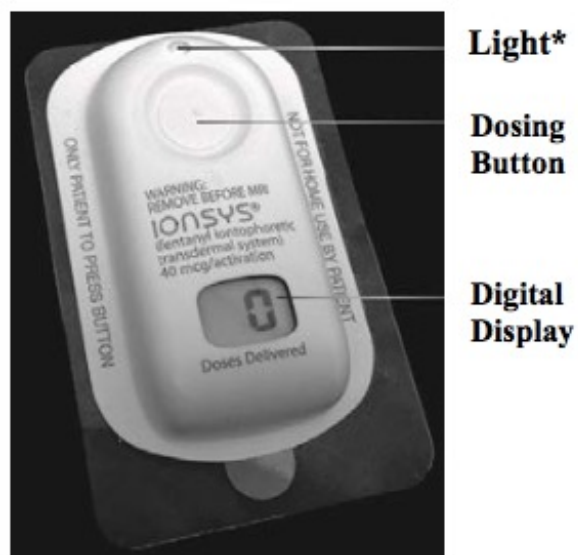
The active ingredient in IONSYS is fentanyl. IONSYS contains 10.8 mg of fentanyl hydrochloride equivalent to 9.7 mg of fentanyl. IONSYS is designed to deliver a 40 mcg dose of fentanyl (equivalent to 44.4 mcg of fentanyl hydrochloride) over a 10-minute period upon each activation of the dose button [see *Dosage and Administration* (2.2)].

The inactive ingredients in the IONSYS hydrogels consist of cetylpyridinium chloride, USP; citric acid, USP; polacrilin; polyvinyl alcohol; sodium citrate, USP; sodium chloride, USP; sodium hydroxide; and purified water, USP.

11.2 System Components and Structure

Each IONSYS (see Figure 8) is composed of a plastic top housing that contains the battery and electronics and a red plastic bottom housing containing two hydrogel reservoirs and a polyisobutylene skin adhesive. Only one of the hydrogels (the anode, located under the dosing button) contains fentanyl HCl, along with inactive ingredients. The other hydrogel (the cathode) contains only pharmacologically inactive ingredients. The bottom housing has a red tab that is used for IONSYS removal from the skin and during disposal [see *Dosage and Administration* (2.3, 2.4)]. A siliconized clear, plastic release liner covers the hydrogels and must be removed and discarded prior to placement on the skin. IONSYS is powered by a 3-volt lithium battery.

Figure 8 IONSYS[®] (fentanyl iontophoretic transdermal system)



*Light is off or on (blinks and displays red or green color light)

12. CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Fentanyl is an opioid analgesic. Fentanyl interacts predominantly with the μ -opioid receptor. These μ -

binding sites are discretely distributed in the human brain, spinal cord, and other tissues.

12.2 Pharmacodynamics

Analgesia

In clinical settings, fentanyl exerts its principal pharmacologic effects on the central nervous system. Its primary actions of therapeutic value are analgesia and sedation. Fentanyl may increase the patient's tolerance for pain and decrease the perception of suffering, although the presence of the pain itself may still be recognized. When patients titrated themselves to analgesic effect with IONSYS, serum concentrations were in the range of 0.4 to 1.5 ng/mL over the 24-hour dosing period.

Respiratory Effects

Hypoventilation can occur throughout the therapeutic range of fentanyl serum concentrations and may occur at any time during therapy, especially for patients who have an underlying pulmonary condition or who receive doses of opioids or other CNS drugs associated with hypoventilation in addition to IONSYS. The respiratory effects of IONSYS should be monitored by clinical evaluation, including oxygen saturation, respiratory rate, and degree of sedation. After delivery of the maximum number of doses in the shortest possible time period (80 consecutive doses delivered over approximately 13 hours), the fentanyl serum concentration was in the range of 1.51 to 2.37 ng/mL, which is in the range that could result in respiratory depression [*see Warnings and Precautions (5.1) and Overdosage (10)*].

Effects on the Cardiovascular System

Fentanyl may produce orthostatic hypotension and fainting. Histamine assays and skin wheal testing in humans indicate that clinically significant histamine release rarely occurs with fentanyl administration. Assays in humans show no clinically significant histamine release in dosages up to 50 mcg/kg.

Effects on Central Nervous System

Central nervous system effects, such as sedation and depression of respiration, increase with increasing serum fentanyl concentrations. In addition to analgesia, alterations in mood, euphoria and dysphoria, and drowsiness commonly occur. Fentanyl depresses the respiratory centers and the cough reflex, and constricts the pupils. Analgesic blood concentrations of fentanyl may cause nausea and vomiting by directly stimulating the chemoreceptor trigger zone, but nausea and vomiting are significantly more common in ambulatory than in recumbent patients, as is postural syncope.

Effects on Gastrointestinal Tract and Other Smooth Muscle

Opioids increase the tone and decrease the propulsive contractions of the smooth muscle of the gastrointestinal tract. The resultant prolongation in gastrointestinal transit time may be responsible for the constipating effect of opioids. Because opioids may increase biliary tract pressure, some patients with biliary colic may experience worsening rather than relief of pain.

While opioids generally increase the tone of urinary tract smooth muscle, the net effect tends to be variable, in some cases producing urinary urgency, in others, difficulty in urination.

12.3 Pharmacokinetics

Unless otherwise specified, the clinical pharmacology studies described in this section were performed in healthy adult volunteers. Volunteers were administered naloxone to antagonize the opioid effects of fentanyl.

Absorption

At the initiation of each dose, an electrical current is activated for 10 minutes, which moves a dose of fentanyl from the drug-containing reservoir through the skin and into the systemic circulation. Compared to IV fentanyl administration, fentanyl concentrations in blood increase slowly with IONSYS activation and continue to increase for approximately 5 minutes after the completion of each 10 minute dose.

The systemic absorption of fentanyl from IONSYS increases as a function of time, and this increase appears to be independent of frequency of dosing. At treatment initiation, the amount of fentanyl absorbed is expected to be approximately 16 mcg (see Figure 9A and Figure 9B). In clinical pharmacokinetic studies, on-demand dosing was initiated immediately after IONSYS application. This resulted in absorption of a 40 mcg fentanyl dose by about 10 hours post treatment initiation. Thereafter, a 40 mcg dose of fentanyl is delivered with each activation.

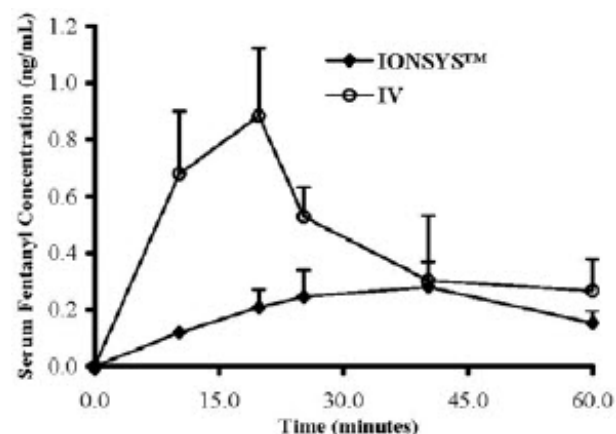
After delivery of the maximum number of doses in the shortest possible time period (80 consecutive doses delivered over approximately 13 hours), the average fentanyl serum concentration was 1.94 ± 0.43 ng/mL. Pharmacokinetic data from illustrative dosing regimens are represented in Table 2. When IONSYS was applied without activating the current, the average absorption rate for fentanyl over 24 hours was 2.3 mcg/h.

Inter-subject variability in fentanyl AUC following IONSYS treatment (33%) was comparable to IV fentanyl treatment (28%).

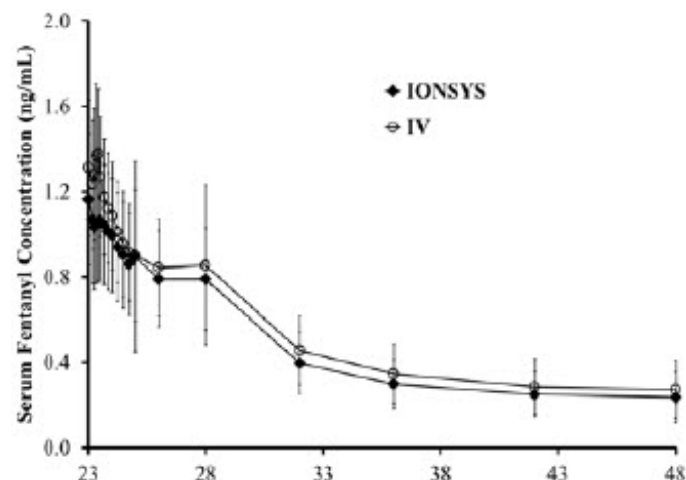
The delivery of fentanyl from IONSYS is similar whether applied on the upper outer arm or the chest. When IONSYS is placed on the lower inner arm, the delivery of fentanyl is approximately 20% lower. Other application sites have not been evaluated.

Figure 9: Serum Fentanyl Concentration Following 40 mcg IONSYS[®] (fentanyl) Compared to IV Fentanyl

A: First Hour of a Representative Treatment *



B: Last Hour and Upon Termination of a Representative Treatment *



* IONSYS[®] 40 mcg: 2 sequential doses over 20 minutes every hour for 23 hours and 20 minutes; IV: 80 mcg dose over 20 minutes every hour for 23 hours and 20 minutes.

Table 2: Mean Pharmacokinetic Parameters Based on Representative and Maximum Dosing

Regimens (n=23)

	Dosing Regimen	
Parameter	48 ^a doses (two sequential doses every hour for 23 hours and 20 minutes)	80 ^b sequential doses (one dose every ten minutes for 13 hours and 20 minutes)
AUC per on demand dose (ng/mL)	0.57±0.13	0.51±0.16
Cmax (ng/mL)	1.3±0.3	1.94±0.43

AUC for this dosing regimen is value estimated between 23-24 hours

Average AUC over all doses delivered during the treatment duration (13.33 hours)

^a Representative dosing regimen based on number of doses administered by patients in Phase 3 clinical studies

^b Maximum theoretical dosing

Distribution

Fentanyl administered intravenously exhibits a three-compartment disposition model. In healthy volunteers after IV administration, the estimated initial distribution half-life was about 6 minutes; the second distribution half-life was about 1-hour; and the terminal half-life was about 16 hours. The average volume of distribution for fentanyl at steady state following IV administration is 833 L.

Mean values for unbound fractions of fentanyl in plasma are estimated to be between 13 and 21%. Fentanyl binds to erythrocytes, α_1 -acid glycoproteins, and plasma albumin.

Binding is independent of drug concentration over the therapeutic range. Fentanyl plasma protein binding capacity decreases with increasing ionization of the drug. Alterations in blood pH may alter ionization of fentanyl and therefore its distribution between plasma and the central nervous system. Fentanyl accumulates in the skeletal muscle and fat and is released slowly into the blood.

Elimination

Metabolism

In humans, fentanyl is metabolized primarily by cytochrome P450 3A4-mediated N-dealkylation to norfentanyl and other inactive metabolites that do not contribute materially to the observed activity of the drug. The average clearance in healthy subjects following IV administration was observed to be 53 L/h.

A decline in fentanyl concentration after termination of treatment and the terminal half-life is similar following IV administration of fentanyl and IONSYS (see Figure 9B). This suggests a negligible contribution from continued absorption of fentanyl remaining in the skin.

Skin does not metabolize fentanyl administered transdermally. This was determined in a human keratinocyte cell assay.

Excretion

Within 72 hours of IV fentanyl administration, approximately 75% of the dose is excreted in urine, mostly as metabolites, with less than 10% representing unchanged drug. Approximately 9% of the dose is recovered in the feces, primarily as metabolites.

Specific Populations

Age

Age did not affect fentanyl absorption from IONSYS.

Sex

Sex differences have been reported for hepatically metabolized drugs. Generally, those that are metabolized by CYP3A4 appear to be eliminated faster by women in many cases. There have been no reports on gender differences in fentanyl pharmacokinetics.

Race

Race did not affect fentanyl absorption from IONSYS.

Renal Impairment

No studies specific to IONSYS in patients with renal impairment have been conducted. In the literature, the pharmacokinetics of fentanyl in patients with severe renal disease was compared to healthy patients. Plasma fentanyl concentrations decreased faster following an IV fentanyl administration in those with renal disease than in the control group, indicating more rapid clearance in the former. As renal clearance of fentanyl is only 10%, a decrease in renal function would not be expected to have a significant effect on the clearance of fentanyl.

Hepatic Impairment

No studies specific to IONSYS in patients with hepatic impairment have been conducted. In the literature, fentanyl appears to be affected more by hepatic blood flow than by hepatocellular function. The plasma concentration time profiles for the control and cirrhotic patients were similar and not significantly different with respective average elimination half-life values of 10.8 mL/min/kg vs. 11.3 mL/min/kg and volume of distribution values of 3.81 L/kg vs. 4.41 L/kg. In addition, the pharmacokinetics of fentanyl in patients with end-stage liver disease who were undergoing hemodialysis to those in normal patients was studied. While differences between groups were not statistically significant, fentanyl clearance values were reported to be lower for the hepatically impaired patients.

Drug Interaction Studies

CYP3A4 Inhibitors

Fentanyl is metabolized mainly via the human cytochrome P450 3A4 isoenzyme system (CYP3A4). The interaction between ritonavir, a CYP3A4 inhibitor, and fentanyl was investigated in eleven healthy volunteers in a randomized crossover study. Subjects received oral ritonavir or placebo for 3 days. The ritonavir dose was 200 mg tid on Day 1 and 300 mg tid on Day 2 followed by one morning dose of 300 mg on Day 3. On Day 2, fentanyl was given as a single IV dose at 5 mcg/kg two hours after the afternoon dose of oral ritonavir or placebo. Naloxone was administered to counteract the side effects of fentanyl. The results suggested that ritonavir might decrease the clearance of fentanyl by 67%, resulting in a 174% (range 52%–420%) increase in fentanyl AUC_{0-∞}. The concomitant use of transdermal fentanyl with all CYP3A4 inhibitors (such as ritonavir, ketoconazole, itraconazole, troleandomycin, clarithromycin, nelfinavir, nefazadone, amiodarone, amprenavir, aprepitant, diltiazem, erythromycin, fluconazole, fosamprenavir, verapamil, or grapefruit juice) may result in an increase in fentanyl plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression. Carefully monitor patients receiving IONSYS and any CYP3A4 inhibitor for signs of respiratory depression for an extended period of time and discontinue IONSYS if warranted [see Boxed Warning, Warnings and Precautions (5.15), and Drug Interactions (7.3)].

CYP3A4 Inducers

Co-administration with agents that induce CYP3A4 activity may decrease plasma concentration of fentanyl following use of IONSYS. Discontinuation of a concomitantly used cytochrome P450 3A4 inducer may result in an increase in fentanyl plasma concentration.

13. NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

In a two-year carcinogenicity study conducted in rats, fentanyl was not associated with an increased incidence of tumors at subcutaneous doses up to 0.033 mg/kg/day in males or 0.1 mg/kg/day in females. These lifetime doses in rats are approximately 0.1 and 0.3, respectively, the maximum recommended human dose (MRHD) of 3.2 mg/day by transdermal administration based on a mg/m² body surface area

comparison and a 60 kg human body weight.

Mutagenesis

Fentanyl is not mutagenic in the in vitro bacterial reverse mutation assay (Ames assay), the primary rat hepatocyte unscheduled DNA synthesis assay, the BALB/c 3T3 transformation test, and the in vitro chromosomal aberration assays using either human lymphocytes or Chinese hamster ovary cells.

Impairment of Fertility

The potential effects of fentanyl on male and female fertility were examined in the rat model via two separate experiments. In the male fertility study, male rats were treated with fentanyl doses of 0, 0.025, 0.1, or 0.4 mg/kg/day (equivalent to 0.08, 0.3, 1.2 times, respectively, the MHRD) via continuous intravenous infusion for 28 days prior to mating; female rats were not treated. In the female fertility study, female rats were treated with fentanyl doses of 0, 0.025, 0.1, or 0.4 mg/kg/day (equivalent to 0.08, 0.3, 1.2 times, respectively, the MHRD) via continuous intravenous infusion for 14 days prior to mating until Day 16 of pregnancy; male rats were not treated. Analysis of fertility parameters in both studies indicated that an intravenous dose of fentanyl up to 0.4 mg/kg/day to either the male or the female alone produced no effects on fertility (this dose is approximately 1.2 times the maximum available daily human dose on a mg/m² basis). In a separate study, a single daily bolus dose of fentanyl was shown to impair fertility in rats when given in intravenous doses of 0.3 times the MRHD for a period of 12 days.

14. CLINICAL STUDIES

14.1 Placebo-Controlled Trials

The efficacy and safety of IONSYS for treatment of short-term acute pain were evaluated in three placebo-controlled studies in postoperative patients. The patients were predominantly female (70–83%) and Caucasian (79–84%), and their mean age was 45–54 years (range, 18–90 years). Patients were enrolled while in the recovery room shortly after major surgery (predominantly lower abdominal or orthopedic) if they were expected to require at least 24 hours of parenteral opioid treatment and were not opioid tolerant; their ASA (American Society of Anesthesiologists) physical status was I, II, or III; and their postsurgical recovery was expected to be uncomplicated. Across the trials, 154 patients were ASA I status (21%); 435 patients were ASA II status (60%); and 138 patients were ASA III status (19%). Administration of long-lasting or continuous regional analgesics, or any non-opioid analgesics, was not permitted in the studies. Patients who remained in the studies for three or more hours using IONSYS (or the control) for patient-controlled analgesia (PCA) were considered evaluable.

In the immediate postoperative period, patients were titrated to comfort with IV fentanyl or morphine per hospital protocol. Once comfortable, patients were randomized and IONSYS or matching placebo IONSYS was applied. Patients were instructed to use IONSYS for pain. Supplemental IV fentanyl was administered by bolus injection as needed to achieve comfort up to three hours post-enrollment. The percentage of patients who used rescue medication during these three hours, as well as the mean amount of rescue medication used, is shown in Table 3 below.

Table 3: Percentage of Patients Requiring Supplemental IV Fentanyl Medication in Hours 0–3 (Mean Quantity Administered) in Studies 1, 2, and 3

Study	IONSYS n=454	Placebo n=273
Study 1	45% (83 mcg)	52% (102 mcg)
Study 2	48% (100 mcg)	55% (95 mcg)
Study 3	34% (78 mcg)	36% (76 mcg)

After Study Hour 3, IONSYS alone or the placebo treatment alone was used to provide analgesia. Efficacy demonstrated in all three studies as demonstrated by the last mean pain intensity scores recorded during the 24-hour treatment period are presented in Table 4.

Table 4: Mean Pain Intensity Score in Studies 1, 2, and 3

Study	IONSYS n=454	Placebo n=273	p-value
Study 1 (NRS ^a)	3.4	5.3	<0.0001
Study 2 (VAS ^b)	31	41	0.0474
Study 3 (VAS ^b)	21	37	0.0006

^a Verbal numerical rating scale 0-10 at 24 hours or at discontinuation

^b Visual analogue scale, 0-100 mm at 24 hours or at discontinuation

In each of the three randomized, double-blind, placebo-controlled trials, fewer patients discontinued for lack of efficacy from three hours to twenty-four hours after IONSYS application (see Table 5).

Table 5: Percentage of Patients Who Withdrew due to Inadequate Analgesia in Studies 1, 2, and 3

Study	IONSYS n=454	Placebo n=273	p-value
Study 1	27% (64/235)	57% (116/204)	<0.0001
Study 2	25% (36/142)	40% (19/47)	0.049
Study 3	8% (6/77)	41% (9/22)	0.0001

The efficacy of IONSYS was similar across the range of body mass indices studied (<25 to >40 kg/m² Body Mass Index).

Patients who completed 24 hours of IONSYS treatment in the controlled studies used a wide range of the available 80 doses, with a mean of 29 doses per patient (range of 0 to 93 doses). The majority of patients (56.5%) used between 11 to 50 doses. One percent of patients required a second IONSYS within 24 hours, after exhausting the first IONSYS.

16. HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

IONSYS (fentanyl iontophoretic transdermal system) is packaged in a sealed tray containing one Controller and one pouched Drug Unit for assembly. For distribution, there are six sealed trays per carton.

NDC 65293-011-06 (carton of six trays containing IONSYS)

16.2 Storage and Handling

Accidental contact with the hydrogels (on the adhesive side of IONSYS) can result in fatal overdose of fentanyl. Therefore, the IONSYS must only be handled while wearing gloves. If there is accidental contact with skin, the affected area should be rinsed thoroughly with water. Do not use

soap, alcohol, or other solvents to remove the hydrogel because they may enhance the drug's ability to penetrate the skin [see *Warnings and Precautions* (5.1)].

IONSYS should be stored at 25°C (77°F); excursions permitted to 15–30°C (59–86°F). Assemble and use immediately after removal from the individually sealed package. Do not use if the seal on the Tray or Drug Unit pouch is broken or damaged.

16.3 Disposal

To dispose of a used IONSYS:

1. With gloves on, pull the red tab to separate the red bottom housing containing fentanyl from IONSYS (see Figure 7a).
2. Fold the red housing in half with the sticky side facing in (see Figure 7b).
3. Dispose of the folded over red housing containing the residual fentanyl per your institution's procedures or by flushing it down the toilet. This step should be witnessed by a second health care provider. The used bottom housing of IONSYS contains fentanyl that could be harmful or fatal if ingested.
4. Hold down dosing button until the display goes blank and then dispose of rest of IONSYS containing electronics in waste designated for batteries.

17. PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (IONSYS Guide for Patients).

Life-Threatening Respiratory Depression

- Discuss the risk of respiratory depression with patients, explaining that the risk is greatest when starting IONSYS. Advise patients how to recognize respiratory depression and to seek medical attention if they are experiencing breathing difficulties.
- Advise patients not to leave the hospital with an IONSYS [see *Warnings and Precautions* (5.1)].
- Advise patients not to let anyone else activate the dosing button on the IONSYS since only the patient knows how much pain he or she is experiencing. Patients should be cautioned that allowing others to activate the device may result in a potentially fatal overdose [see *Dosage and Administration* (2.1)].
- Advise patients not to give IONSYS to other people, as it may lead to a fatal overdose of fentanyl.

Accidental Exposure

- Advise patients not to let anyone touch IONSYS if it falls off accidentally and to contact their nurse, pharmacist, or doctor immediately. Accidental exposure to the fentanyl hydrogel may result in a fatal overdose of fentanyl.
- Instruct patients not to remove or reposition IONSYS and that IONSYS must be removed only by medical personnel [see *Warnings and Precautions* (5.1)].
- Instruct patients not to touch the sticky side of IONSYS and not to touch the gels. Caution patients that fentanyl is rapidly absorbed by the eyes and mouth and could be harmful or fatal if absorbed this way. Advise patients to inform a health care provider if accidental exposure occurs and to immediately rinse the affected area with copious amounts of water. Soap, alcohol, or other solvents should not be used because they may enhance permeability [see *Warnings and Precautions* (5.1)].
- Instruct patients to keep IONSYS out of the reach of children at all times [see *Warnings and Precautions* (5.1)].

Addiction, Abuse and Misuse

- Inform patients that the use of IONSYS, even when taken as recommended can result in addiction, abuse and misuse, which can lead to overdose and death [see *Warnings and Precautions* (5.3)].

Anaphylaxis

- Advise patients to inform the health care provider of any allergies to fentanyl, cetylpyridinium

chloride (e.g., Cepacol[®]), or any components of IONSYS.

Administration Instructions

- Advise patients that the level of current (62 microA/cm²) provided by IONSYS is generally imperceptible to the patient.

Manufactured, Distributed and Marketed by:

The Medicines Company
8 Sylvan Way
Parsippany, NJ 07054

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IONSYS[®] Important Device Instructions

1 EXPLANATION OF STANDARDIZED MEDICAL DEVICE SYMBOLS

Standardized symbols refer to specific warnings, features, or classifications of the device component of IONSYS[®] (fentanyl iontophoretic transdermal system). See Table 1 for the symbols and meaning of these symbols.

Table 1: Standardized Medical Device Symbols for IONSYS

Symbol	Meaning
	Do not use
	Operating instructions
	Caution
IP54	Dust-protected Protected against splashing water
	Type body floating (BF) applied part*
	Electrostatic discharge (ESD) sensitivity

	Magnetic resonance (MR) unsafe
	Radio frequency (RF) transmitter

*Body floating (BF) refers to a device that comes into contact with the patient's body and allows for electrical conductivity.

2 SYSTEM COMPONENTS AND STRUCTURE

Each IONSYS (see Figure 1) is composed of a plastic top housing that contains the battery and electronics and a red plastic bottom housing containing two hydrogel reservoirs and a polyisobutylene skin adhesive. Only one of the hydrogels (the anode, located under the dosing button) contains fentanyl HCl, along with inactive ingredients. The other hydrogel (the cathode) contains only pharmacologically inactive ingredients. The bottom housing has a red tab that is used only for IONSYS removal from the skin and during disposal. A siliconized clear, plastic release liner covers the hydrogels and must be removed and discarded prior to placement on the skin. IONSYS is powered by a 3-volt lithium battery.

Figure 1 IONSYS[®] (fentanyl iontophoretic transdermal system)



* Light is off or on (blinks and displays red or green color light).

3 IONSYS TROUBLESHOOTING

IONSYS delivers an on-demand dose of fentanyl over 10 minutes. The Normal IONSYS Feedback table (see Table 2) below illustrates normal audible and visual feedback from IONSYS upon assembly and during patient use.

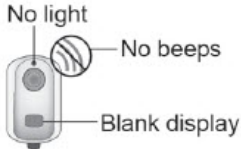
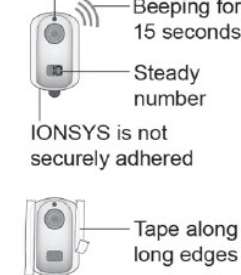
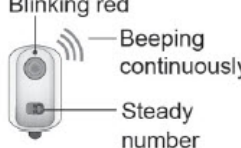
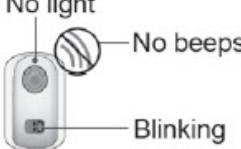
Table 2: Normal IONSYS Feedback During Assembly and Patient Use

Mode	Audible Feedback	Visual Feedback (Light)	Visual Feedback (Digital Display)
Assemble IONSYS by snapping the two parts together	A single audible beep	Light will blink RED momentarily and then start blinking GREEN at a slow rate	Display will flash "88" and then transition to steady "0" indicating that IONSYS is ready for use and 0 doses have been delivered
Ready Mode: IONSYS is ready and awaiting patient request for dose	None	Light will blink GREEN at a slow rate	Display will show the number of doses delivered (steady; not flashing)

Patient initiates a dose by pressing and releasing the button twice within 3 seconds	A single audible beep indicates the start of delivery of each dose	The light changes from blinking GREEN at a slow rate to blinking GREEN at a fast rate	The display alternates between a walking circle and the number of doses delivered
10-minute dose is complete – IONSYS returns to Ready Mode	None	Light changes from blinking GREEN at a fast rate to blinking GREEN at a slow rate	Display will show the number of doses delivered (steady; not flashing)
End of Use: 24 hours or 80 doses have been completed	None	None. Light will be Off.	Display will flash the number of doses delivered

If IONSYS does not appear to function immediately, instruct the patient to attempt to initiate a dose again by firmly pressing and releasing the button twice within 3 seconds (i.e., double-press). A single audible beep will be emitted immediately, confirming that IONSYS is functional. Anytime during use, if IONSYS does not function properly, instruct the patient to call a staff member. Refer to the Error Messages table (see Table 3) for possible problems and appropriate course of action. Error messages provide information (e.g., blinking lights, audible beeps) about problems that may occur during operation of IONSYS.

Table 3: IONSYS Error Messages: Blinking Lights and Audible Beeps

Error Message/Feedback	Probable Cause	Action Required
	Low battery or defective IONSYS	<ol style="list-style-type: none"> 1. Do not use IONSYS. 2. Dispose of IONSYS. 3. Place a new IONSYS on a different skin site.
	Poor skin contact	<ol style="list-style-type: none"> 1. If IONSYS appears to be loose or lifting from skin, secure IONSYS to patient's skin by pressing the edges with fingers or securing with non-allergenic tape. 2. If using tape, apply it along the long edges to secure IONSYS to patient's skin. Do not cover button or display. 3. After taping, if IONSYS beeps again, remove and dispose. Place a new IONSYS on a different skin site. 4. Do not tape if evidence of blistered or broken skin.
	System error	<ol style="list-style-type: none"> 1. Remove IONSYS from patient. 2. Hold down dosing button until beeping stops and display goes blank. 3. Dispose of IONSYS. 4. Place a new IONSYS on a different skin site.
	End of use (24 hours or 80 doses elapsed)	<ol style="list-style-type: none"> 1. Remove IONSYS from patient. 2. Hold down dosing button until display goes blank. 3. Dispose of IONSYS. 4. Place a new IONSYS on a different skin site.

Electromagnetic Compatibility testing for Immunity, specifically, Electrostatic Discharge (ESD) testing, demonstrated contact discharges to the hydrogel touch points caused IONSYS to shut down in a safe mode in several cases. A safe mode is a mode in which the controller cannot be activated; thereby, unable to dispense the drug. Therefore, IONSYS that shut down due to an ESD event are non-operable and deemed defective. These ESD events only occurred during the task of assembling the controller and drug units together.

4 ELECTROMAGNETIC COMPATIBILITY

IONSYS is designed to be used only in a hospital environment. In this environment IONSYS was not shown to interfere with nearby electronic equipment, and is immune to interference from other electronic equipment. IONSYS was tested in compliance with IEC 60601-1-2 at test levels for a hospital environment. Table 4, Table 5, and Table 6 list tests performed and provide guidance on the environment.

Some diagnostic or therapeutic procedures (such as MRI, cardioversion, defibrillation, X-ray, CT, or diathermy), and some electronic security systems can exceed the test levels shown in the tables. Remove IONSYS before exposure to MRI, cardioversion, defibrillation, X-ray, CT, or diathermy. IONSYS contains radio-opaque components and may interfere with an X-ray image or CT scan. Avoid exposing IONSYS to electronic security systems. Electrostatic discharge can exceed the test levels shown in the tables. Avoid contact with synthetic materials (such as carpeted flooring) to reduce the possibility of electrostatic discharge. Communications equipment (such as base stations for radio telephones and land mobile radios, amateur radio, AM and FM radio broadcast and TV broadcast and Radio), and Radio Frequency Identification (RFID) transmitters, can exceed the test levels shown in the tables.




Minimize exposure to sources of electromagnetic radiation by adhering to the separation distances found in Table 6. If exposure to the procedures, electronic security systems, electrostatic discharge, communications equipment, or RFID systems occurs, and if IONSYS does not appear to function normally as described in Table 2, IONSYS should be removed and replaced with a new IONSYS.

Table 4: Guidance and Manufacturer's Declaration - Electromagnetic Emissions

IONSYS is intended for use in the electromagnetic environment specified below. The health care provider should assure that IONSYS is used in such an environment.		
Emission Test	Compliance	Electromagnetic Environment - Guidance
RF emissions CISPR 11	Group 1	IONSYS uses RF energy only for its internal function. Therefore, its RF emissions are very low and are not likely to cause any interference in nearby electronic equipment.
RF emissions CISPR 11	Class B	IONSYS is suitable for use in all establishments, including domestic establishments and those directly connected to the public low-voltage power supply network that supplies buildings used for domestic purposes. NOTE: IONSYS is indicated for hospital use only.

Table 5: Guidance and Manufacturer's Declaration - Electromagnetic Immunity

IONSYS is intended for use in the electromagnetic environment specified below. The health care provider should assure that IONSYS is used in such an environment.			
Immunity Test	IEC 60601 Test Level	Compliance Level	Electromagnetic Environment - Guidance
Electrostatic	1, CLAT		Floors should be wood, concrete, or ceramic tile. If floors are

Discharge (ESD) IEC 61000-4-2	$\pm 6\text{ kV}$ contact $\pm 8\text{ kV}$ air	$\pm 6\text{ kV}$ contact $\pm 8\text{ kV}$ air	covered with synthetic material, the relative humidity should be at least 30%. 
Power frequency (50/60Hz) magnetic field IEC 61000-4-8	3 A/m	3 A/m	Power frequency magnetic fields should be at levels characteristic of a typical location in a typical hospital environment. (a) IONSYS is MR UNSAFE. Remove IONSYS before an MRI procedure. 
Radiated RF IEC 61000-4-3	3 V/m 80 MHz to 2.5 GHz	3 V/m 80 MHz to 2.5 GHz	RF communications equipment and RFID transmitters should be used no closer to IONSYS than the recommended separation distance calculated from the equation applicable to the frequency of the transmitter.(a) Recommended separation distance: $d = 1.2\sqrt{P}$ 150 KHz to 800 MHz $d = 2.3\sqrt{P}$ 800 MHz to 2.5 GHz Where P is the maximum power output of the transmitter in watts (W) according to the transmitter manufacturer and d is the recommended separation distance in meters (m). Interference may occur in the vicinity of equipment marked with the following symbol: 

(a) Field strengths, as determined by an electromagnetic site survey, must be less than the stated compliance level. Remove IONSYS to prevent exposure to field strengths that exceed the stated compliance level.

Table 6: Recommended Separation Distances between RF Transmitters and IONSYS

IONSYS is intended for use in an electromagnetic environment in which radiated RF disturbances are controlled. The health care provider can help prevent electromagnetic interference by maintaining a minimum distance (meters) between RF transmitters and IONSYS as recommended below, according to the maximum output power (watts) of the transmitter.		
Rated maximum output power of transmitter (watts)	Separation distance according to frequency of transmitter (meters)	
	150 kHz to 800 MHz	800 MHz to 2.5 GHz
0.01	0.12	0.23
0.1	0.38	0.73
1	1.2	2.3
10	3.8	7.3
100	12	23
For transmitters rated at a maximum output power not listed above, the recommended separation distance d in meters (m) can be estimated using the equation applicable to the frequency of the transmitter, where P is the maximum output power rating of the transmitter in watts (W) according to the transmitter manufacturer.		

NOTE: For 1W RFID transmitters, the recommended separation distance is 2.3 meters.
NOTE: At 800 MHz, the separation distance for the higher frequency range applies.
NOTE: These guidelines may not apply in all situations. Electromagnetic propagation is affected by absorption and reflection from structures, objects, and people.

For questions about IONSYS, including product returns, call 1-877-488-6835.

Manufactured, Distributed and Marketed by:

The Medicines Company
8 Sylvan Way
Parsippany, NJ 07054

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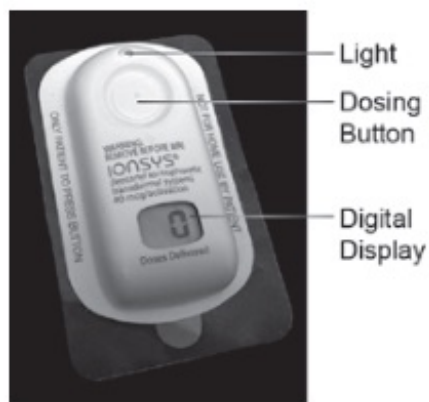
IONSYS Guide for Patients

IONSYS[®] (eye-AHN-sis)

(fentanyl iontophoretic transdermal system) CII

Important:

- **IONSYS is only for use in the hospital. Do not leave the hospital with an IONSYS on your skin.**
- **IONSYS can cause life-threatening breathing problems or death if it is used other than described in the section “How do I use IONSYS?” below.**
- **Keep IONSYS out of the reach of children.**



What is IONSYS?

IONSYS:

- contains the prescription medicine, fentanyl. Fentanyl is a very strong narcotic pain medicine (opioid).
- is only used in the hospital for adults with short-term pain after surgery.
- is a patient-controlled medicine system that sticks to the skin. It will be applied by your healthcare provider on your upper outer arm or chest.

Do not use IONSYS if you are allergic to:

- fentanyl
- Cepacol (cetylpyridinium chloride)

Your healthcare provider:

- will tell you about IONSYS and teach you how to use it.
- will put IONSYS on the skin (of your chest or upper outer arm) after your surgery.
- will control pain from your surgery with other pain medicines until you are awake enough to use IONSYS.
- will check you for side effects from IONSYS.
- must replace your IONSYS as needed. You should not replace your IONSYS yourself.
- will remove your IONSYS before you leave the hospital. **Do not leave the hospital with an IONSYS on your skin.**

How do I use IONSYS?

- You can push the IONSYS dosing button when you are experiencing pain or just before you do an activity that may increase your pain - such as physical therapy or getting out of bed.
- To get a dose of pain medicine from IONSYS, **press and release the dosing button twice within 3 seconds.**



- When you push the dosing button you will hear a single beep and the green light will start blinking quickly. The green light will continue to blink quickly for the 10 minutes it takes to deliver a dose of IONSYS.
- During this time, IONSYS will not deliver another dose even if you press the dosing button again.
- IONSYS can only be activated every 10 minutes.
- When IONSYS is finished delivering a dose, the green light will start blinking slowly. This means you can give yourself more pain medicine, if needed. Just press and release the dosing button twice within 3 seconds like you did before. The digital display will tell your healthcare provider how many doses you have received. Each IONSYS may be used for up to 24 hours or a maximum of 80 doses, whichever comes first.
- If IONSYS starts beeping at any time tell your healthcare provider right away.
- Tell your healthcare provider right away if:
 - you have any questions about IONSYS
 - you are still having pain
 - IONSYS falls off your skin
 - you have trouble using IONSYS

Your healthcare provider will check your IONSYS to make sure it is working properly.

Do not:

- Do not let anyone else press the IONSYS dosing button for you. **You are the only person who should push the dosing button.**
- Do not touch IONSYS if it falls off of your skin. Tell your healthcare provider right away if your IONSYS comes off of your skin. Rinse your hands with water (do not use soap) right away if you accidentally touch the sticky side of IONSYS, and tell your healthcare provider right away.
- Do not let others touch IONSYS.
- Do not remove or replace IONSYS yourself.

- Do not leave the hospital with an IONSYS on your skin. **Make sure your healthcare provider removes your IONSYS before you leave the hospital.**
- **IONSYS is MR Unsafe and should not be brought into an MRI environment.**

Manufactured, Distributed and Marketed by:

The Medicines Company
8 Sylvan Way
Parsippany, NJ 07054

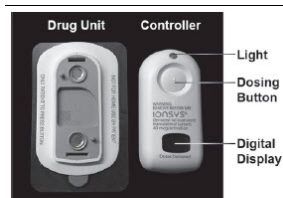
April 2015

Part No. 306-0001 Rev 01

Software Version: 205-0002, SB-SWC-002 Rev. 5, IT101 Controller Software, Version 1.6.715

Printed in USA

Instructions for Use and Disposal



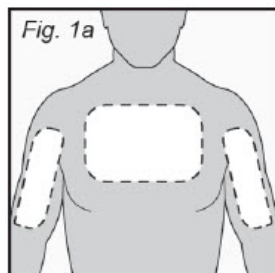
IONSYS[®]

fentanyl iontophoretic transdermal system, 40mcg/activation

For single use only. Up to 24 hours or 80 doses, whichever comes first.

Refer to the Prescribing Information (PI) and the following educational materials for more information about IONSYS:

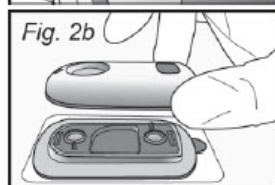
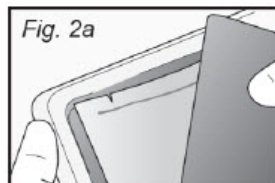
- *IONSYS Guide for Patients*
- *IONSYS REMS Safety Brochure: Guide for Nurses and Pharmacists*



1. Prepare Patient Site

!ONLY 1 IONSYS system should be applied at any given time.

- Choose healthy, unbroken skin on the upper outer arm or chest **ONLY** (see Figure 1a).
- Clip excessive hair if necessary.
Do not shave—this irritates skin.
- Clean with alcohol and let dry.
Do not use soaps, lotions, or other agents.
- When replacing an IONSYS system, the new system must be applied to a different site on the upper outer arm or chest.



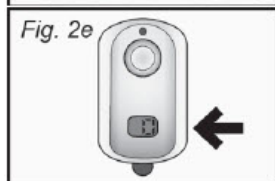
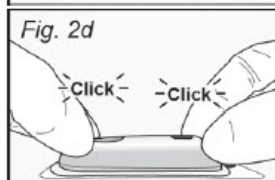
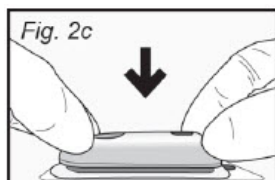
2. Assemble IONSYS

!Always wear gloves when handling IONSYS.

!Complete this step *before* applying IONSYS to patient.

- Peel back tray lid (see Figure 2a). Remove foil pouch and the controller.
- Remove drug unit from foil pouch and place on a hard, flat surface (see Figure 2b).

Continued on next panel.

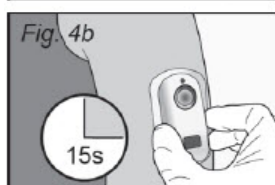
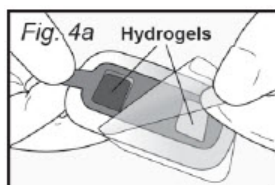


2. Assemble IONSYS (cont.)

- Align the matching shapes (*see Figure 2c*).
- Press on both ends of the device to ensure that snaps at both ends are fully engaged (*see Figure 2d*).
- Wait for system to complete self test and the digital display to read “0” (*see Figure 2e*).

3. Train Patient on Proper Use of IONSYS

*!Refer to the **IONSYS Guide for Patients** to counsel your patient on the safe use of IONSYS.*



4. Apply IONSYS to Patient

! Always wear gloves when handling IONSYS.

- Peel off clear liner and apply IONSYS to the prepared site (*see Figure 4a*).
- Press and hold IONSYS onto patient for **15 seconds** by pressing the edges with fingers (*see Figure 4b*). **Do not press dosing button.**
- If IONSYS is not securely adhered, see IONSYS Troubleshooting – Poor skin contact.

NOTE: Ensure proper display orientation by reading "Doses Delivered" printed below the digital display.



5. Verify Proper Use of IONSYS

*!Remember that **ONLY** the patient should press the dosing button.*

!Remove before MRI or radiographic procedures as medically necessary.

- Patient will initiate a dose by pressing and releasing the button twice in 3 seconds.
- Each dose will be delivered over 10 minutes. During this time IONSYS is locked-out and will not respond to additional button presses.
- During the 10 minutes the light will blink green at a fast rate and the display will alternate between a walking circle and the number of doses delivered (*see Figure 5*).



6. Remove IONSYS from Patient and Dispose

!Follow your institution's procedures for handling narcotics or refer to the PI for more information.

!Always wear gloves when handling IONSYS.

!Important: If drug gel contacts your skin, thoroughly rinse area with water. Do not use soap.

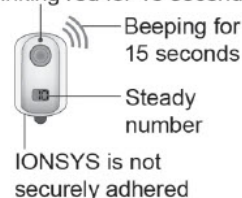
- With gloves on, remove IONSYS from the patient (see Figure 6a).
- Pull the red tab to separate the red housing containing the drug (see Figure 6b).
- Fold the red housing in half and dispose per your institution's procedures or flush down the toilet (see Figure 6c).
- Hold down dosing button until display goes blank and dispose in waste designated for batteries.

IONSYS Troubleshooting

After successful assembly or anytime during use:

If you see or hear this ... then do this :

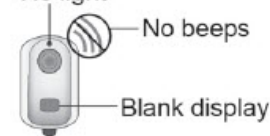
Blinking red for 15 seconds



Poor Skin Contact

- If IONSYS appears to be loose or lifting from skin, secure it to patient's skin by pressing the edges with fingers or securing with nonallergenic tape.
- If using tape, apply it along the long edges to secure IONSYS to patient's skin. ***Do not cover the button or display.***
- After taping, If IONSYS beeps again, remove and dispose. Place a **new** IONSYS on a **different** skin site.
- Do not tape if evidence of blistered or broken skin.***

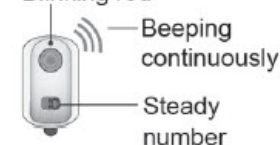
No light



Low Battery or Defective System

- Do not use the system.***
- Dispose of IONSYS per instructions in section 6.
- Place a **new** IONSYS on a **different** skin site.

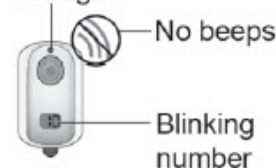
Blinking red



System Error

- Remove from patient.
- Hold down dosing button until beeping stops and display goes blank.
- Dispose of IONSYS per instructions in section 6.
- Place a **new** IONSYS on a **different** skin site.

No light



End-of-Use (80 doses or 24 hours)

Remove from patient.
Hold down dosing button until display goes blank.
Dispose of IONSYS per instructions in section 6.
Place a **new** IONSYS on a **different** skin site.

6835
Fax: 1-877-488-
8601

PRINCIPAL DISPLAY PANEL - IONSYS[®] - Carton

IONSYS[®]
(fentanyl iontophoretic
transdermal system) 

NDC 65293-011-06

**Contains 6 Systems
Rx Only**

Storage

Store at 25°C (77°F)
Excursion permitted to 15-30°C (59-86°F)
Store in the original tray

**DO NOT USE IF SEAL ON TRAY OR
POUCH IS BROKEN OR DAMAGED**

Dosage and Administration

For transdermal use
Use immediately after removal from pouch
See accompanying product literature

Each activation delivers
40 mcg of fentanyl over 10 minutes.
No more than 6 doses/hour can
be delivered. A maximum of
80 doses/system can be delivered
over 24 hours

**See full Prescribing Information
for disposal instructions**

**The
Medicines
Company**

**IONSYS[®] CII
(fentanyl iontophoretic transdermal system)**

**The
Medicines
Company**

NDC 65293-011-06

**Contains 6 Systems
Rx Only**

Storage

Store at 25°C (77°F)

Excursion permitted to 15-30°C (59-86°F)

Store in the original tray

DO NOT USE IF SEAL ON TRAY OR POUCH IS BROKEN OR DAMAGED

Dosage and Administration

For transdermal use

Use immediately after removal from pouch

See accompanying product literature

Each activation delivers 40 mcg of fentanyl over 10 minutes. No more than 6 doses/hour can be delivered. A maximum of 80 doses/system can be delivered over 24 hours

See full Prescribing Information for disposal instructions

PRINCIPAL DISPLAY PANEL - IONSYS® - Label



IONSYS® CII

(fentanyl iontophoretic transdermal system)

40 mcg/activation

(equivalent to fentanyl HCl 44.4 mcg)

For hospital use only

Each activation delivers 40 mcg of fentanyl over 10 minutes. No more than 6 doses can be delivered in one hour. Maximum of 80 doses/system over 24 hours. Each system contains 10.8 mg fentanyl HCl

NDC 65293-011-01

Tray contains one Drug Unit and one Controller

Rx Only

Store in the original tray

Store at 25°C (77°F)

Excursion permitted to 15-30°C (59-86°F)

DO NOT USE IF SEAL ON TRAY OR POUCH IS BROKEN OR DAMAGED
KEEP OUT OF REACH OF CHILDREN

See full Prescribing Information for disposal instructions

Manufactured, Distributed and Marketed by:
The Medicines Company
Parsippany, NJ 07054

IONSYS

fentanyl iontophoretic transdermal system patch

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:65293-011
Route of Administration	TRANSDERMAL	DEA Schedule	CII

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
FENTANYL HYDROCHLORIDE (UNII: 59H156XY46) (FENTANYL - UNII:UF599785JZ)	FENTANYL	40 ug

Inactive Ingredients

Ingredient Name	Strength
CETYL PYRIDINIUM CHLORIDE (UNII: D9OM4SK49P)	
CITRIC ACID MONOHYDRATE (UNII: 2968PHW8QP)	
POLACRILIN (UNII: RCZ785HI7S)	
POLYVINYL ALCOHOL (UNII: 532B59J990)	
SODIUM CITRATE (UNII: 1Q73Q2JULR)	
SODIUM CHLORIDE (UNII: 451W47IQ8X)	
SODIUM HYDROXIDE (UNII: 55X04QC32I)	
WATER (UNII: 059QF0K00R)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:65293-011-06	6 in 1 CARTON	06/01/2015	
1	NDC:65293-011-01	1 in 1 TRAY		
1		1 in 1 POUCH; Type 2: Prefilled Drug Delivery Device/System (syringe, patch, etc.)		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA021338	06/01/2015	

Labeler - The Medicines Company (040861601)

Registrant - The Medicines Company (040861601)

Establishment

Name	Address	ID/FEI	Business Operations
DPT Lakewood LLC		077744035	manufacture(65293-011) , pack(65293-011)

Establishment

Name	Address	ID/FEI	Business Operations
Intertek USA Inc.		805606758	manufacture(65293-011)

Establishment

Name	Address	ID/FEI	Business Operations
Johnson Matthey Pharmaceutical Materials		808176705	api manufacture(65293-011)

Revised: 5/2015

The Medicines Company